General

Guideline Title

AASLD guidelines for treatment of chronic hepatitis B.

Bibliographic Source(s)

Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016 Jan;63(1):261-83. [132 references] PubMed

Guideline Status

This is the current release of this guideline.

This updates a previous version: Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology. 2009 Sep;50(3):661-2. [304 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Recommendations are followed by quality of evidence ratings (High, Moderate, Low, and Very Low), and the strength of the recommendations (Strong or Conditional) which are defined at the end of the "Major Recommendations" field.

Note from the National Guideline Clearinghouse (NGC): Technical remarks designed to facilitate implementation accompany each recommendation and can be found in the original guideline document.

Treatment of Persons with Immune-Active Chronic Hepatitis B (CHB)

The American Association for the Study of Liver Diseases (AASLD) recommends antiviral therapy for adults with immune-active CHB (hepatitis B e antigen [HBeAg] negative or HBeAg positive) to decrease the risk of liver-related complications. (Quality/Certainty of Evidence: Moderate, Strength of Recommendation: Strong)

The AASLD recommends pegylated interferon (Peg-IFN), entecavir, or tenofovir as preferred initial therapy for adults with immune-active CHB. (Quality/Certainty of Evidence: Low, Strength of Recommendation: Strong)

Treatment of Adults with Immune-Tolerant CHB

The AASLD recommends against antiviral therapy for adults with immune-tolerant CHB. (Quality/Certainty of Evidence: Moderate, Strength of Recommendation: Strong)

The AASLD suggests that alanine aminotransferase (ALT) levels be tested at least every 6 months for adults with immune-tolerant CHB to monitor for potential transition to immune-active or -inactive CHB. (Quality/Certainty of Evidence: Very low, Strength of Recommendation: Conditional)

The AASLD suggests antiviral therapy in the select group of adults >40 years of age with normal ALT and elevated hepatitis B virus deoxyribonucleic acid (HBV DNA) (≥1,000,000 IU/mL) and liver biopsy showing significant necroinflammation or fibrosis. (Quality/Certainty of Evidence: Very low, Strength of Recommendation: Conditional)

Treatment of HBeAg Positive Immune-Active Chronic Hepatitis Persons Who Seroconvert to Anti-HBe on Nucleos(t)ide Analog (NA) Therapy

The AASLD suggests that HBeAg-positive adults without cirrhosis with CHB who seroconvert to anti-HBe on therapy discontinue NAs after a period of treatment consolidation. (Quality/Certainty of Evidence: Very Low, Strength of Recommendation: Conditional)

The AASLD suggests indefinite antiviral therapy for HBeAg-positive adults with cirrhosis with CHB who seroconvert to anti-HBe on NA therapy, based on concerns for potential clinical decompensation and death, unless there is a strong competing rationale for treatment discontinuation. (Quality/Certainty of Evidence: Very Low, Strength of Recommendation: Conditional)

Duration of Treatment in Persons with HBeAg-Negative Immune-Active CHB

The AASLD suggests indefinite antiviral therapy for adults with HBeAg-negative immune-active CHB unless there is a competing rationale for treatment discontinuation. (Quality/Certainty of Evidence: Low, Strength of Recommendation: Conditional)

Renal and Bone Disease in Persons on NA Therapy

The AASLD suggests no preference between entecavir and tenofovir regarding potential long-term risks of renal and bone complications. (Quality/Certainty of Evidence: Very Low (bone); Low (renal), Strength of Recommendation: Conditional)

Management of Persons with Persistent Low-Level Viremia on NA Therapy

The AASLD suggests that persons with persistent low level viremia (<2,000 IU/mL) on entecavir or tenofovir monotherapy continue monotherapy, regardless of ALT. (Quality/Certainty of Evidence: Very Low, Strength of Recommendation: Conditional)

The AASLD suggests one of two strategies in persons with virological breakthrough on entecavir or tenofovir monotherapy: either switch to another antiviral monotherapy with high barrier to resistance or add a second antiviral drug that lacks cross-resistance. (Quality/Certainty of Evidence: Very Low, Strength of Recommendation: Conditional)

Management of Adults with Cirrhosis and Low-Level Viremia

The AASLD suggests that adults with compensated cirrhosis and low levels of viremia (<2,000 IU/ mL) be treated with antiviral therapy to reduce the risk of decompensation, regardless of ALT level. (Quality/Certainty of Evidence: Very Low, Strength of Recommendation: Conditional)

The AASLD recommends that hepatitis B surface antigen (HBsAg)-positive adults with decompensated cirrhosis be treated with antiviral therapy indefinitely regardless of HBV DNA level, HBeAg status, or ALT level to decrease risk of worsening liver-related complications. (Quality/Certainty of Evidence: Moderate, Strength of Recommendation: Strong)

Treatment of CHB in Pregnancy

The AASLD suggests antiviral therapy to reduce the risk of perinatal transmission of hepatitis B in HBsAg-positive pregnant women with an HBV DNA level >200,000 IU/mL. (Quality/Certainty of Evidence: Low, Strength of Recommendation: Conditional)

The AASLD recommends against the use of antiviral therapy to reduce the risk of perinatal transmission of hepatitis B in the HBsAg-positive pregnant woman with an HBV DNA ≤200,000 IU/mL. (Quality/Certainty of Evidence: Low, Strength of Recommendation: Strong)

Treatment of CHB in Children

The AASLD suggests antiviral therapy in HBeAg-positive children (ages 2 to <18 years) with both elevated ALT and measurable HBV DNA levels, with the goal of achieving sustained HBeAg seroconversion. (Quality/Certainty of Evidence: Moderate, Strength of Recommendation: Conditional)

The AASLD recommends against use of antiviral therapy in HBeAg-positive children (ages 2 to <18 years) with persistently normal ALT, regardless of HBV DNA level. (Quality/Certainty of Evidence: Very Low, Strength of Recommendation: Strong)

Definitions

Rating the Quality of Evidence

Study Design	Initial Rating of Quality of Evidence	Rate Down When	Rate Up When
Randomized controlled trials (RCTs)	High Moderate	Risk of bias Inconsistency Imprecision Indirectness Publication bias	Large effect (e.g., relative risk [RR]: 0.5) Very large effect (e.g., RR: 0.2) Dose response gradient All plausible confounding would increase the association
Observational	Low Very low		

Determinants of the Strength of a Recommendation

- Quality of evidence
- Balance of benefits and harms
- Patient values and preferences
- Resources and costs

Implications of the Strength of Recommendation

Strong	• Population: Most people in this situation would want the recommended course of action and only a small proportion would not. • Health care workers: Most people should receive the recommended course of action. • Policy makers: The recommendation can be adapted as a policy in most situations.
Conditional	• Population: The majority of people in this situation would want the recommended course of action, but many would not. • Health care workers: Be prepared to help patients make a decision that is consistent with their values using decision aids and shared decision making. • Policy makers: There is a need for substantial debate and involvement of stakeholders.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Chronic hepatitis B (CHB) virus (HBV) infection

Note: Management of hepatitis B in patients waiting for liver transplantation and prevention of recurrent hepatitis B post-liver transplant will not be discussed in these guidelines.

Guideline Category

Management

Risk Assessment

Treatment

Clinical Specialty

Family Practice

Gastroenterology

Infectious Diseases

Internal Medicine

Obstetrics and Gynecology

Pediatrics

Intended Users

Advanced Practice Nurses

Health Care Providers

Nurses

Physician Assistants

Physicians

Public Health Departments

Guideline Objective(s)

To present official recommendations of the American Association for the Study of Liver Diseases (AASLD) on the treatment of chronic hepatitis B (CHB) virus (HBV) infection in adults and children

Target Population

Adults and children with chronic hepatitis B (CHB) virus (HBV) infection

Interventions and Practices Considered

1. Treatment of persons with immune-active chronic hepatitis B (CHB) (antiviral therapy [pegylated interferon (Peg-IFN)], entecavir, or tenofovir)
2. Management of adults with immune-tolerant CHB
    - Monitoring of alanine aminotransferase (ALT) levels
    - Antiviral therapy (as indicated)
3. Treatment of hepatitis B e antigen (HBeAg) positive immune-active chronic hepatitis persons who seroconvert to anti-HBe on nucleos(t)ide analog (NA) therapy
    - Discontinuation of NA after period of treatment consolidation
    - Indefinite antiviral therapy
4. Duration of treatment in persons with HBeAg-negative immune-active CHB (indefinite antiviral therapy)
5. Management of persons with persistent low-level viremia on NA therapy
    - Continuation of monotherapy (entecavir or tenofovir)
    - Switching to another antiviral monotherapy with high barrier to resistance
    - Adding a second antiviral drug that lacks cross-resistance
6. Management of adults with cirrhosis and low-level viremia (antiviral therapy)
7. Treatment of CHB in pregnancy (antiviral therapy)
8. Treatment of CHB in children (antiviral therapy)

Major Outcomes Considered

- Cirrhosis
- Decompensation
- Hepatocellular carcinoma (HCC)
- Death
- Loss of hepatitis B surface antigen (HbsAg)
- Reactivation
- Seroreversion
- Renal function
- Hypophosphatemia
- Bone health
- Hepatitis B virus (HBV) resistance
- Clinical flare
- Loss of hepatitis B e antigen (HBeAg)
- Chronic hepatitis B (CHB) virus in the infant
- Maternal and fetal/infant safety

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

A methodologist moderated and facilitated the process of question development. A separate group of American Association for the Study of Liver Diseases (AASLD) content experts collaborated with an independent research group with expertise in conducting systematic reviews to synthesize the available evidence informing the key questions. See the original guideline document for the key questions and see the "Availability of Companion Documents" field for the systematic reviews.

Antiviral Therapy in Chronic Hepatitis B Viral Infection during Pregnancy: A Systematic Review and Meta-analysis

Eligibility Criteria

The systematic review group included controlled or comparative studies that enrolled pregnant women diagnosed with chronic hepatitis B (CHB) virus (HBV) infection (characterized by the presence of hepatitis B surface antigen [HBsAg] for more than 6 months), who received antiviral therapy and reported the outcomes of interest, including prevention of mother-to-child-transmission (MTCT) of HBV, clinical efficacy, and adverse outcomes from antiviral therapy to both mothers and newborns. Both English and non-English-language studies were included. The systematic review group excluded studies that enrolled infants who did not receive immunization during the first week postpartum; studies of patients coinfected with hepatitis C, hepatitis D, or human immunodeficiency virus (HIV); patients receiving steroids, chemotherapy/immunotherapy, liver transplantation, and hemodialysis; and uncontrolled studies or studies published as abstracts only.

Search Strategy

A comprehensive search of Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, and Scopus was conducted from early 1988 to September 11, 2014. The search strategy was designed and conducted by an experienced librarian with input from the principal investigator. Controlled vocabulary supplemented with keywords was used to search for studies of antivirals for hepatitis B in pregnancy. Details of the search strategy are available in Supporting Table 1 of the systematic review. A manual search of bibliographies of the included studies and relevant systematic reviews was conducted. Content experts from the American Association for the Study of Liver Diseases (AASLD) were also queried for potential references.

Study Selection

Two independent reviewers screened titles and abstracts for potential eligibility in duplicate using an online reference management system (DistillerSR; Evidence Partners, Inc.). Included abstracts were then reviewed in full text following the same procedure. Disagreements were reconciled by consensus or by a third reviewer.

Antiviral Therapy in Management of Chronic Hepatitis B Viral Infection in Children: A Systematic Review and Meta-analysis

Eligibility Criteria

The systematic review group included studies that enrolled children (<18 years) with chronic HBV infection treated with antiviral therapy. Due to the anticipated limited number of randomized controlled trials (RCTs) evaluating patient-important (clinical) outcomes, the group included observational studies that evaluated such outcomes. Outcomes of interest were cirrhosis, decompensated liver disease, hepatocellular carcinoma (HCC), alanine aminotransferase (ALT) normalization, HBV deoxyribonucleic acid (DNA) suppression, hepatitis B e antigen/hepatitis B surface antigen (HBeAg/HBsAg) seroconversion, and HBeAg/HBsAg loss. They included both English and non-English-language studies. They excluded studies enrolling adults; patients coinfected with hepatitis C, hepatitis D, or HIV; patients receiving combination therapy, steroids, or chemotherapy/immunotherapy; liver transplant recipients; and hemodialysis patients. Supporting Table S1 of the systematic review describes the detailed inclusion and exclusion criteria.

Search Strategy

The search strategy was designed and conducted by an experienced librarian with input from the principal investigator. A comprehensive search of Medline In-Process & Other Non-Indexed Citations, MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and Scopus was conducted from January 1988 to December 2, 2014. Controlled vocabulary supplemented with keywords was used to search for studies of antiviral therapy for hepatitis B in children. Supporting Table S2 of the systematic review provides details of the search strategy. The systematic review group conducted a manual search of bibliographies of the included studies and previous systematic reviews to identify relevant studies. Content experts from the AASLD were also queried for potential references.

Study Selections

Using an online reference management system (DistillerSR; Evidence Partners, Inc.), two reviewers independently screened titles and abstracts. Full texts of the included abstracts were retrieved and screened in duplicate. Disagreements were harmonized by consensus or arbitration by a third reviewer. The Committee calculated interrater agreement (kappa) during the full text screening to observe the agreement between reviewers.

Antiviral Therapy for Chronic Hepatitis B Viral Infection in Adults: A Systematic Review and Meta-analysis

Eligibility Criteria

The systematic review group included RCTs and controlled observational studies that enrolled adults ≥18 years old diagnosed with chronic HBV infection who received antiviral therapy. They excluded studies that included patients with acute HBV infection; patients who were pregnant; patients coinfected with hepatitis C or D or HIV; patients receiving corticosteroids, chemotherapy, or immunosuppressive therapy; transplant recipients; and hemodialysis patients, as well as studies without control or comparison groups. Supporting Table S1 of the systematic review summarizes the inclusion and exclusion criteria for each key question.

Search Strategy

An experienced Mayo Clinic librarian conducted a comprehensive search of Medline In-Process & Other Non-Indexed Citations, MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Scopus from early 1988 to September 16, 2014. Controlled vocabulary supplemented with keywords was used to search for comparative studies of antivirals for CHB. No language restrictions were used. Members from the AASLD HBV guideline methodology and writing committees helped identify additional studies. Supporting Table S2 of the systematic review specifies the detailed search strategy.

Study Selections

Two reviewers independently screened titles and abstracts for potential eligibility using an online reference management system (DistillerSR; Evidence Partners, Inc.). Full texts of the included abstracts were retrieved and screened in duplicate. Disagreements were resolved by seeking consensus or arbitration by a third reviewer. Interreviewer agreement (kappa) was calculated during each screening level to assess agreement between reviewers. For Population Intervention Comparison Outcome questions where no studies meeting the predefined criteria were found, the AASLD HBV guideline methodology committee performed manual searches for uncontrolled observational studies. Data from these studies were

summarized narratively and in general consistent with low-quality evidence.

Number of Source Documents

Antiviral Therapy in Chronic Hepatitis B Viral Infection during Pregnancy: A Systematic Review and Meta-analysis

The initial search resulted in 734 citations and three systematic reviews that included the China Biological Medicine Database and summarized additional studies published in Chinese. The committee eventually included 26 studies. The average weighted kappa for study selection was 0.82. The study selection process and reasons for exclusions are depicted in Figure 1 of the systematic review (see the "Availability of Companion Documents" field).

Antiviral Therapy in Management of Chronic Hepatitis B Viral Infection in Children: A Systematic Review and Meta-analysis

From the 2321 citations identified with the primary search strategy, 14 studies that enrolled 1425 children were finally included. Two studies evaluated the clinical (patient-important) outcomes of death, cirrhosis, and HCC and 12 studies reported intermediate outcomes. Average weighted kappa (interrater agreement) for study selection was 0.75. Details of study selection and reasons for exclusion are described in Figure 1 of the systematic review (see the "Availability of Companion Documents" field).

Antiviral Therapy for Chronic Hepatitis B Viral Infection in Adults: A Systematic Review and Meta-analysis

A total of 73 studies were included. Figure 1 of the systematic review (see the "Availability of Companion Documents" field) describes the details of the selection process. The average weighted kappa for study selection was 0.78. Controlled studies that reported the outcomes of interest were only available for questions 1, 2, 3, and 5. Uncontrolled studies that are relevant to questions 4, 6, and 7 are summarized in Supporting Information. Supporting Table S4 in the systematic review provides the Grading of Recommendations Assessment, Development and Evaluation (GRADE) summary of the evidence.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Rating the Quality of Evidence

Study Design	Initial Rating of Quality of Evidence	Rate Down When	Rate Up When
Randomized controlled trials (RCTs)	High Moderate	Risk of bias Inconsistency Imprecision Indirectness Publication bias	Large effect (e.g., relative risk [RR]: 0.5) Very large effect (e.g., RR: 0.2) Dose response gradient All plausible confounding would increase the association
Observational	Low Very low		

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

See the "Availability of Companion Documents" field for the systematic reviews commissioned to support this guideline.

Antiviral Therapy in Chronic Hepatitis B Viral Infection during Pregnancy: A Systematic Review and Meta-analysis

Data Extraction

For each study, data extraction was done in duplicate using a standardized, pretested form. A third reviewer compared data and resolved inconsistencies by referring to the full text of the articles. The systematic review group extracted the following data from each study: study characteristics, patient baseline characteristics, intervention details, and outcomes of interest.

Outcomes

The systematic review group was interested in the following outcomes: infant outcomes including the risk of mother-to-child transmission (MTCT) transmission, defined by hepatitis B surface antigen (HBsAg) seropositivity at 6-12 months or hepatitis B virus deoxyribonucleic acid (HBV DNA) positivity at 6-12 months; Apgar score (1 minute); prematurity rate; and congenital malformation rate. Maternal outcomes included HBV DNA suppression, alanine aminotransferase (ALT) normalization, hepatitis B e antigen (HBeAg) loss, HBeAg seroconversion, cesarean section rate, postpartum hemorrhage rate, and elevated creatine kinase.

Risk of Bias Assessment

Two reviewers independently assessed the risk of bias (i.e., systematic error) using the Cochrane Risk of Bias assessment tool and the Newcastle-Ottawa Scale for randomized controlled trials (RCTs) and observational studies, respectively. The quality of evidence (i.e., certainty in the estimates) was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Criteria used to evaluate quality of evidence were risk of bias, indirectness (surrogate outcomes), imprecision (wide confidence intervals), inconsistency (heterogeneity), and publication bias.

Statistical Analysis

For dichotomized outcomes, the systematic review group calculated the risk ratio (RR) and 95% confidence intervals (CIs) using binomial distribution. They then pooled the log-transformed RRs using the DerSimonian and Laird random-effect models and estimated heterogeneity using the Mantel-Haenszel model. For continuous outcomes, the committee calculated the weighted difference in means between the baseline and the longest duration of follow-up for each study and the pooled effect size using the DerSimonian and Laird random-effect model. To measure the overall heterogeneity across the included studies, the systematic review group used the I^2 statistic, where I^2 >50% suggests high heterogeneity. All statistical analyses were conducted using STATA, version 13 (StataCorp LP, College Station, TX). They planned to explore the impact of publication bias using the Egger regression asymmetry test and constructing funnel plots if a sufficient number of studies (>20) per outcome was available and heterogeneity was low.

Antiviral Therapy in Management of Chronic Hepatitis B Viral Infection in Children: A Systematic Review and Meta-analysis

Data Extraction

Data extraction was done in duplicate using a standardized, piloted form. A third reviewer compared the reviewers' entered data and resolved any inconsistencies by referring to the full text of the article. The systematic review group extracted the following variables from each study: study characteristics, patient baseline characteristics, intervention details, and outcomes of interest.

Risk of Bias Assessment

Two reviewers independently assessed the risk of bias (i.e., systematic error) using the Cochrane risk of bias tool and the Newcastle-Ottawa Scale for RCTs and observational studies. Quality of evidence (i.e., certainty in the estimates) was evaluated using the GRADE approach. Criteria used to evaluate quality of evidence were risk of bias, indirectness (surrogate outcomes), imprecision (wide confidence intervals), inconsistency (heterogeneity), and publication bias.

Statistical Analysis

For dichotomized outcomes, the systematic review group calculated RRs and 95% CIs using binomial distribution. They then pooled the log-transformed RRs using the DerSimonian and Laird random-effect method with the heterogeneity estimated from the Mantel-Haenszel model. To measure the overall heterogeneity across the included studies, they calculated the I^2 statistic, with I^2 >50% suggesting high heterogeneity. All statistical analyses were conducted using STATA, version 13 (StataCorp LP, College Station, TX). The systematic review group explored the impact of publication bias using the Egger regression asymmetry test and by constructing funnel plots if a sufficient number of studies (>20) per outcome was available and heterogeneity was low.

Antiviral Therapy for Chronic Hepatitis B Viral Infection in Adults: A Systematic Review and Meta-analysis

Data Extraction

Data extraction was done using a standardized, piloted form. The systematic review group extracted data on study characteristics, patient characteristics, intervention details, and outcomes of interest.

Methodological Quality and Risk of Bias Assessment

The systematic review group used the Cochrane Risk of Bias assessment tool and modified Newcastle-Ottawa Scale to assess the risk of bias in RCTs and observational studies, respectively. Quality of evidence (i.e., certainty in the estimates) was evaluated using the GRADE approach. Criteria used to evaluate quality of evidence were risk of bias, indirectness (surrogate outcomes), imprecision (wide confidence intervals), inconsistency (heterogeneity), and publication bias.

Statistical Analysis

For dichotomized outcomes, the systematic review group calculated RRs and 95% CIs using binomial distribution. They then pooled the log-transformed RRs using the DerSimonian and Laird random-effects models and estimated heterogeneity using the Mantel-Haenszel model. To measure the overall heterogeneity across the included studies, the systematic review group calculated the I^2 statistic, where I^2 >50% suggests a high degree of heterogeneity. All statistical analyses were conducted using STATA, version 13 (StataCorp LP, College Station, TX). To explore heterogeneity, they conducted subgroup analysis for studies enrolling patients with more advanced liver disease; they performed stratified analysis for the following groups: compensated cirrhosis, decompensated cirrhosis, acute on chronic liver failure, and severe acute exacerbations of chronic hepatitis B (CHB). The systematic review group explored the impact of publication bias using the Egger regression asymmetry test and constructing funnel plots if a sufficient number of studies (>20) per outcome was available and heterogeneity was low.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

A methodologist moderated and facilitated the process of question development. A separate group of American Association for the Study of Liver Diseases (AASLD) content experts collaborated with an independent research group with expertise in conducting systematic reviews to synthesize the available evidence informing these key questions. By multiple face-to-face meetings, phone conferences, and electronic communication, the systematic review group finalized evidence summaries following the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. In this approach, the quality of evidence (i.e., certainty in evidence) is rated as high, moderate, low, or very low based on the domains of precision, directness, consistency, and risk of bias and publication bias. The guideline-writing group based its recommendations on the quality of evidence, balance of benefits and harms, patients' values and preferences, and clinical context. Recommendations are graded as strong (apply to most patients with minimal variation) or conditional (apply to the majority of patients whose values and preferences are consistent with the course of action). Technical remarks are added to recommendations to facilitate implementation. Evidence profiles corresponding to five of the key questions are presented as an appendix to the original guideline document. For the remaining questions with sparse and indirect evidence, relevant studies are summarized after each recommendation (see the original guideline document).

Rating Scheme for the Strength of the Recommendations

Determinants of the Strength of a Recommendation

- Quality of evidence
- Balance of benefits and harms
- Patient values and preferences
- Resources and costs

Implications of the Strength of Recommendation

Strong	• Population: Most people in this situation would want the recommended course of action and only a small proportion would not. • Health care workers: Most people should receive the recommended course of action.

	• Policy makers: The recommendation can be adapted as a policy in most situations.
Conditional	• Population: The majority of people in this situation would want the recommended course of action, but many would not. • Health care workers: Be prepared to help patients make a decision that is consistent with their values using decision aids and shared decision making. • Policy makers: There is a need for substantial debate and involvement of stakeholders.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

This Practice Guideline was approved by the American Association for the Study of Liver Diseases (AASLD) on August 1, 2015.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Clearance of hepatitis B surface antigen (HBsAg), whether spontaneous or after antiviral therapy, reduces risk of hepatic decompensation and improves survival.
- Patient selection and timing of treatment are critical decisions in order to avoid overtreatment, maximize therapeutic benefit while limiting duration of therapy, and minimize risk for antiviral drug resistance later in life.
- Antiviral therapy in patients with immune active chronic hepatitis B (CHB) virus (HBV) infection can reduce the risk of cirrhosis, decompensated liver disease, and hepatocellular carcinoma.
- In immune tolerant patients, moderate-quality evidence supports improved intermediate outcomes with antiviral therapy.
- Antiviral therapy improves HBV suppression and reduces mother to child transmission (MTCT) in women with chronic HBV infection with high viral load compared to the use of hepatitis B immunoglobulin and vaccination alone; the use of telbivudine, lamivudine, and tenofovir appears to be safe in pregnancy with no increased adverse maternal or fetal outcome.

Potential Harms

Overall, all nucleos(t)ide analogs (NAs) have an excellent safety profile across a wide spectrum of persons with chronic hepatitis B (CHB), including those with decompensated cirrhosis and transplant recipients. The side effects listed below for NAs are infrequent.

- Pegylated interferon (Peg-IFN)-2a (adult): Flu-like symptoms, fatigue, mood disturbances, cytopenias, autoimmune disorders in adults,
- IFN-α-2b (children): Anorexia and weight loss
- Lamivudine: Pancreatitis, lactic acidosis

- Telbivudine: Creatine kinase elevations and myopathy, peripheral neuropathy, lactic acidosis
- Entecavir: Lactic acidosis
- Adefovir: Acute renal failure, Fanconi syndrome, nephrogenic diabetes insipidus, lactic acidosis
- Tenofovir: Nephropathy, Fanconi syndrome, osteomalacia, lactic acidosis

Contraindications

Contraindications

- Pegylated interferon (Peg-IFN) is contraindicated in persons with autoimmune disease, uncontrolled psychiatric disease, cytopenias, severe cardiac disease, uncontrolled seizures, and decompensated cirrhosis.
- The safety of entecavir in pregnancy is not known and IFN therapy is contraindicated.

Qualifying Statements

Qualifying Statements

- This document presents official recommendations of the American Association for the Study of Liver Diseases (AASLD) on the treatment of chronic hepatitis B (CHB) virus (HBV) infection in adults and children. Unlike previous AASLD practice guidelines, this guideline was developed in compliance with the Institute of Medicine standards for trustworthy practice guidelines and uses the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach. Multiple systematic reviews of the literature were conducted to support the recommendations in this practice guideline. An enhanced understanding of this guideline will be obtained by reading the applicable portions of the systematic reviews.
- This guideline focuses on using antiviral therapy in chronic HBV infection and does not address other related and important issues, such as screening, prevention, and surveillance. For broader issues related to diagnosis, surveillance, and prevention as well as treatment in special populations (e.g., liver transplant recipients) that are not addressed by this guideline, the previous AASLD guideline and recent World Health Organization (WHO) guideline are excellent additional resources.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016 Jan;63(1):261-83. [132 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2016 Jan

Guideline Developer(s)

American Association for the Study of Liver Diseases - Nonprofit Research Organization

Source(s) of Funding

The funding for the development of this Practice Guideline was provided by the American Association for the Study of Liver Diseases.

Guideline Committee

Practice Guidelines Committee

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Potential Conflict of Interest

Dr. Jonas consults and received grants from Gilead. She received grants from Bristol-Myers Squibb and Roche. Dr. Chang advises Genentech,

Alnylam, and Arbutus. Dr. Terrault consults for Bristol-Myers Squibb and received grants from Gilead. Dr. Bzowej received grants from Gilead, Synageva, and Ocera.

Guideline Status

This is the current release of this guideline.

This updates a previous version: Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology. 2009 Sep;50(3):661-2. [304 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Hepatology Web site .

Availability of Companion Documents

The following are available:

- Lok AS, McMahon BJ, Brown RS Jr, Wong JB, Ahmed AT, Farah W, Almasri J, Alahdab F, Benkhadra K, Mouchli MA, Singh S, Mohamed EA, Abu Dabrh AM, Prokop LJ, Wang Z, Murad MH, Mohammed K. Antiviral therapy for chronic hepatitis B viral infection in adults: a systematic review and meta-analysis. Hepatology. 2016 Jan;63(1):284-306. Available from the Hepatology Web site .
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Patient Resources

None available

NGC Status

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